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APPLICATION NUMBER:

21-124

MEDICAL REVIEW

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MEDICAL OFFICER'S REVIEW OF NDA 21-124
ORIGINAL SUBMISSION

JAN 31 2000

November 15, 1999

SPONSOR: Novartis Pharmaceuticals
East Hanover, New Jersey

DRUG: Terbinafine hydrochloride solution 1%

TRADE NAME: Lamisil AT Smart Pump

REASON FOR NDA: Rx to OTC switch

CURRENT Rx INDICATIONS: Tinea pedis, tinea cruris, tinea corporis, tinea versicolor.

PROPOSED OTC INDICATIONS: Athlete's foot (interdigital), jock itch, ringworm

Labeling claims:
- cures athlete's foot (tinea pedis)
- cures jock itch (tinea cruris) and ringworm (tinea corporis)
- relieves itching, burning, cracking and scaling which accompany these conditions

DOSAGE AND ADMINISTRATION: Topical spray applications BID for one week for athlete's foot; QD for one week for jock itch and ringworm.

RELATED NDA: NDA 20-749 for prescription use of Lamisil solution 1%; approved for tinea pedis, tinea cruris, tinea corporis, and tinea versicolor.

PHARMACOLOGY AND CONTROLS REVIEWS: These are currently pending.

Index
Medical Officer's review of NDA 21-124

Background

Four formulations of Lamisil are currently approved; these are Lamisil cream 1%, Lamisil emulsion gel 1%, Lamisil solution/spray 1%, and Lamisil tablets. Lamisil tablets were approved in 1996 for the treatment of onychomycosis; Lamisil cream was approved in 1992 for prescription treatment of tinea pedis, cruris, and corporis, and tinea versicolor, and in 1999 for OTC treatment of athlete's foot, jock itch, and ringworm; Lamisil solution/spray was approved in 1997; Lamisil emulsion gel was approved in 1998 for prescription treatment of tinea pedis, cruris, and corporis, and tinea versicolor.

Contents of NDA

In support of an Rx to OTC switch for Lamisil solution, the following material is included in the NDA.

a. US and worldwide marketing status and distribution data for terbinafine HCl solution from 1997 through 1998.
b. Synopses of the clinical studies which support the safety and efficacy of Lamisil solution for tinea pedis, cruris, and corporis, together with an updated integrated summary of efficacy based on these studies, and re-analyses using an MITT population.
c. Updated integrated summary of safety of all adverse events, including a section on fungal resistance to terbinafine HCl.

Pre-NDA meeting

A pre-NDA meeting was held on 12/21/98, in which the Agency requested that the sponsor include the following information in the NDA.

- a re-analysis of the efficacy data, to be done on the MITT population, defined as all randomized patients.
- an update of the integrated summaries of safety and efficacy, with an emphasis on the tinea cruris safety data, and inclusion of data from the World Health Organization.
- a section on the issue of fungal resistance to terbinafine HCl.

The Agency stated that only interdigital tinea pedis, and not mocassin type tinea pedis, could be listed as an indication in the OTC labeling, as the clinical studies SFF 301 and SFF 351 submitted under NDA 20-749 support the safety and efficacy only in the treatment of interdigital tinea pedis. However, it was noted that the interdigital and plantar forms of tinea pedis have

not been previously differentiated by indication in the OTC marketplace, and that it may be more confusing than helpful to do so now. The Divisions (OTC and DDDDP) suggested a Phase 4 commitment from the sponsor to conduct studies to demonstrate that the product is safe and effective for the entire OTC indication of athlete's foot by demonstrating efficacy and safety in plantar tinea pedis.

US and foreign marketing history

Approximately 1.7 million bottles of terbinafine hydrochloride solution 1% have been sold worldwide since 1997. In the US, where the product was launched in 1998, ——— bottles have been sold.

I. Pivotal clinical studies on dermatophytoses

Lamisil solution/spray 1% was approved under NDA 20-749 on 10/17/97 for the treatment of tinea pedis, tinea cruris, and tinea corporis due to *Trichophyton rubrum, Trichophyton mentagrophytes, or Epidermophyton floccosum*, and for the treatment of tinea versicolor. The approved dosage for tinea corporis and cruris is once daily application for one week, and for tinea pedis is twice daily applications for one week.

The pivotal studies on the dermatophytoses performed under NDA 20-749 were as follows.

Pivotal studies on dermatophytoses in NDA 20-749
Lamisil solution 1%

Indication	Study #	Treatment duration (wks)	# of patients per treatment group *		
			Lamisil QD	Lamisil BID	Placebo
T. Pedis	SFF 351	1		104	49
	SFF 301	1	113		57
T. Corporis /cruris	SFF 303	1	99		48
	SFF 105	1	32		34
	SFF 108	1	35		36

* All patients who had received at least one dose of the study medication and had at least one post-baseline assessment.

Two other controlled studies (# 309 and 104) were performed on tinea pedis; these were not considered by this reviewer to be pivotal. Study # 309 was a comparison of one week of treatment with Lamisil to four weeks of treatment with clotrimazole, and Study # 104 involved QD applications of Lamisil for 2 weeks.

In these studies the efficacy parameters were mycology (KOH exam and culture), a scoring of clinical signs and symptoms, and a clinical assessment by the investigator and the patient. The signs and symptoms evaluated were erythema, desquamation, pruritus, vesicles, encrustation, and pustules; these were scored on a scale of 0=absent, 1=mild, 2=moderate, and 3=severe.

The results of the studies are presented as the percentage of patients with an 'Effective Treatment' and a 'Complete Cure'. The primary efficacy variable was the percentage of patients with Effective Treatment. Effective Treatment was defined as a mycological cure (negative KOH and culture) and a total clinical score representing minimal residual signs and symptoms, namely, a total clinical score of 2 or less for erythema, desquamation, and pruritus, with no score greater than 1 for each individual sign or symptom, and scores of 0 for vesiculation, encrustation, and pustules. Complete Cure was defined as a mycological cure and a complete absence of all signs and symptoms (total clinical score of 0). The investigator and patient clinical assessments were considered to be secondary efficacy variables.

In the current application the results are presented for the ITT population as in the original application, and are additionally provided for the MITT population, in accordance with the Agency request at the pre-NDA meeting. The ITT population is defined as all patients who were randomized, received at least one dose of study medication, were not delayed exclusions, and had at least one non-missing post-baseline efficacy assessment of microscopy, culture, or clinical signs and symptoms. The MITT population is defined as all patients who were randomized; those patients without any post baseline assessments were counted as treatment failures.

In the tables that follow, all results are presented for the ITT population, except for those results designated as the end of study results for the MITT population.

1. Tinea pedis

a. Study SFF 351.

This was a double blind, randomized, multicenter, parallel group

comparison of Lamisil solution 1% with its vehicle in patients with interdigital tinea pedis, with twice daily applications for 7 days. The results were as follows.

Mycological organism at baseline Study 351 - Tinea pedis				
	E. Floccosum	T. Mentagrophytes	T. Rubrum	Other
Lamisil	1 (2%)	4 (7%)	52 (90%)	1
Vehicle	1 (4%)	4 (14%)	23 (82%)	0

Mycological cure Study 351 - Tinea pedis			
	Lamisil	Vehicle	p value
Week 1	24/56 (43%)	4/28 (14%)	0.008
Week 2	34/57 (60%)	3/25 (12%)	< 0.001
Week 4	43/55 (78%)	3/24 (13%)	< 0.001
Week 8	47/54 (87%)	3/23 (13%)	< 0.001
End of study	51/58 (88%)	4/28 (14%)	< 0.001

Effective Treatment Study 351 - Tinea pedis			
	Lamisil	Vehicle	p value
Week 1	10/56 (18%)	1/28 (4%)	0.085
Week 2	9/57 (16%)	2/25 (8%)	0.324
Week 4	24/55 (44%)	3/24 (13%)	0.008
Week 8	35/54 (65%)	1/23 (4%)	< 0.001
End of study	38/58 (66%)	1/28 (4%)	< 0.001
End of study (MITT)	60/104 (58%)	4/49 (8%)	< 0.001

Complete Cure Study 351 - Tinea pedis			
	Lamisil	Vehicle	p value
Week 1	1/56 (2%)	1/28 (4%)	0.615
Week 2	1/57 (2%)	1/25 (4%)	0.513
Week 4	1/55 (2%)	0/24 (0%)	0.460
Week 8	11/54 (20%)	0/23 (0%)	0.020
End of study	12/58 (21%)	0/28 (0%)	0.007
End of study (MITT)	26/104 (25%)	3/49 (6%)	0.002

b. Study SFF 301.

This was a double blind, randomized, multicenter, parallel group comparison of Lamisil solution 1% with its vehicle in patients with interdigital tinea pedis, with once daily applications for 7 days. The results were as follows.

Mycological organism at baseline Study 301 - Tinea pedis				
	E. Floccosum	T. Mentagrophytes	T. Rubrum	Other
Lamisil	6 (8%)	13 (18%)	50 (70%)	3 (4%)
Vehicle	2 (5%)	12 (31%)	25 (64%)	-

Mycological cure Study 301 - Tinea pedis			
	Lamisil	Vehicle	p value
Week 1	34/69 (49%)	5/37 (14%)	0.002
Week 2	36/66 (55%)	6/32 (19%)	0.001
Week 8	50/53 (94%)	8/32 (25%)	< 0.001
End of study	60/71 (85%)	9/39 (23%)	< 0.001

Effective Treatment Study 301 - Tinea pedis			
	Lamisil	Vehicle	p value
Week 1	14/69 (20%)	2/37 (5%)	0.049
Week 2	18/67 (27%)	2/33 (6%)	0.014
Week-8	44/53 (83%)	7/32 (22%)	< 0.001
End of study	54/71 (76%)	8/39 (21%)	< 0.001
End of study (MITT)	76/115 (66%)	16/57 (28%)	< 0.001

Complete Cure Study 301 - Tinea pedis			
	Lamisil	Vehicle	p value
Week 1	2/69 (3%)	0/38 (0%)	0.260
Week 2	8/67 (12%)	1/33 (3%)	0.194
Week 8	29/54 (54%)	2/32 (6%)	< 0.001
End of study	36/71 (51%)	2/39 (5%)	< 0.001
End of study (MITT)	49/115 (43%)	9/57 (16%)	< 0.001

II. Tinea corporis/cruris

Three studies were performed; these were double blind, randomized, multicenter, parallel group comparison of Lamisil solution 1% with its vehicle in patients with tinea corporis/cruris, using once daily applications for 7 days. Results were as follows.

1. Study SFF 303

Mycological organism at baseline Study 303 - Tinea cruris/corporis				
	E. Floccosum	T. Mentagrophytes	T. Rubrum	Other
Lamisil	1 (1%)	7 (10%)	54 (75%)	10
Vehicle	0 (0%)	6 (16%)	24 (65%)	7

Mycological cure Study 303 - Tinea corporis/cruris			
	Lamisil	Vehicle	p value
Week 1	54/69 (78%)	4/36 (11%)	< 0.001
Week 2	53/63 (84%)	9/30 (30%)	< 0.001
Week 4	41/51 (80%)	5/16 (31%)	0.010
Week 8	35/38 (92%)	5/12 (42%)	0.006
End of study	61/72 (85%)	10/36 (28%)	< 0.001

Effective Treatment Study 303 - Tinea corporis/cruris			
	Lamisil	Vehicle	p value
Week 1	26/69 (38%)	0/36 (0%)	< 0.001
Week 2	44/64 (69%)	3/31 (10%)	< 0.001
Week 4	36/51 (71%)	3/16 (19%)	0.007
Week 8	33/39 (85%)	4/12 (33%)	0.013
End of study	51/72 (71%)	4/36 (11%)	< 0.001
End of study (MITT)	71/102 (70%)	84/49 (16%)	< 0.001

Complete Cure Study 303 - Tinea corporis/cruris			
	Lamisil	Vehicle	p value
Week 1	4/70 (6%)	0/36 (0%)	0.102
Week 2	16/65 (25%)	1/31 (3%)	0.022
Week 4	29/53 (55%)	1/16 (6%)	0.008
Week 8	28/40 (70%)	1/12 (8%)	0.016
End of study	38/72 (53%)	1/36 (3%)	< 0.001
End of study (MITT)	51/102 (50%)	4/49 (8%)	< 0.001

2. Study SFF 105

Mycological organism at baseline Study 105 - Tinea cruris/corporis				
	E. Floccosum	T. Mentagrophytes	T. Rubrum	Other
Lamisil	2 (8%)	3 (12%)	18 (69%)	3
Vehicle	0 (0%)	1 (4%)	21 (81%)	4

Mycological cure Study 105 - Tinea corporis/cruris			
	Lamisil	Vehicle	p value
Week 1	10/26 (38%)	6/26 (23%)	0.202
Week 2	17/24 (71%)	8/23 (35%)	0.005
Week 4	18/23 (78%)	5/16 (31%)	0.002
End of study	18/26 (69%)	6/26 (23%)	0.001

Effective Treatment Study 105 - Tinea corporis/cruris			
	Lamisil	Vehicle	p value
Week 1	5/26 (19%)	2/26 (8%)	0.232
Week 2	13/24 (54%)	5/23 (22%)	0.011
Week 4	17/23 (74%)	2/16 (13%)	< 0.001
End of study	17/26 (65%)	2/26 (8%)	< 0.001
End of study (MITT)	22/32 (69%)	5/34 (15%)	< 0.001

Complete Cure Study 105 - Tinea corporis/cruris			
	Lamisil	Vehicle	p value
Week 1	-	-	
Week 2	-	-	
Week 4	10/23 (43%)	2/16 (13%)	ND
End of study	10/26 (38%)	2/26 (8%)	ND
End of study (MITT)	13/32 (41%)	3/34 (9%)	< 0.01

3. Study SFF 108

Mycological organism at baseline Study 108 - Tinea cruris/corporis				
	E. Floccosum	T. Mentagrophytes	T. Rubrum	Other
Lamisil	4 (11%)	0 (0%)	28 (80%)	3
Vehicle	2 (6%)	0 (0%)	31 (89%)	2

Mycological cure Study 108 - Tinea corporis/cruris			
	Lamisil	Vehicle	p value
Week 1	15/32 (47%)	5/34 (15%)	0.005
Week 2	24/29 (83%)	7/33 (21%)	< 0.001
Week 4	21/27 (78%)	9/32 (28%)	< 0.001
End of study	25/33 (76%)	10/35 (29%)	< 0.001

Effective Treatment Study 108 - Tinea corporis/cruris			
	Lamisil	Vehicle	p value
Week 1	9/33 (27%)	2/35 (6%)	0.018
Week 2	17/29 (59%)	4/34 (12%)	< 0.001
Week 4	20/27 (74%)	7/33 (21%)	< 0.001
End of study	22/34 (65%)	7/35 (20%)	< 0.001
End of study (MITT)	22/36 (61%)	7/36 (19%)	< 0.001

Complete Cure Study 108 - Tinea corporis/cruris			
	Lamisil	Vehicle	p value
Week 1	-	-	
Week 2	-	-	
Week 4	14/34 (41%)	2/34 (6%)	ND
End of study	14/34 (41%)	2/35 (6%)	ND
End of study (MITT)	14/36 (39%)	2/36 (6%)	< 0.001

Safety data

1) Integrated Summary of Safety - NDA 20-749

Safety data are provided for Lamisil solution in the following studies: a) adequate and well controlled studies performed on the approved indications, b) placebo controlled studies on other indications, c) uncontrolled studies, and d) clinical pharmacology studies.

a) Adequate and well controlled studies for the approved indications.

Nine adequate and well-controlled studies are provided in NDA 20-749. The indication, treatment frequency and duration, and number of safety subjects in each treatment group in each study were as follows. (Safety subjects were defined as those subjects who received at least one dose of study medication and had at least one post-baseline safety assessment.)

Controlled studies in NDA 20-749 Lamisil solution 1%						
Indication	Study #	Treatment duration (wks)	# of safety subjects per treatment group			
			Lamisil QD	Lamisil BID	Clotrimazole BID	Placebo
P. Versicolor	SFF 353	1		98		47
	SFF 305	1		77		35
T. Pedis	SFF 351	1		104		49
	SFF 301	1	113			57
	SFF 309	1		340	345	
	SFF 104	2	42			42
T. Corporis /cruris	SFF 303	1	99			48
	SFF 105	1	32			34
	SFF 108	1	35			36
Total		US studies	74	202		172
		Non-US studies*	247	417	345	176
		All studies	321	619	345	348
* Non-US studies: # 305, 301, 309, 303, 108						

The adverse event data are presented for each indication. Additionally, six of the nine controlled studies tabulated above, those with SFF 300 numbers, were consistent in design, duration, and conduct, and were pooled for adverse event data. The remaining three studies were of somewhat different design and conduct and were summarized separately.

Pityriasis versicolor: Two studies were performed on this indication, one of which was in the US and one in Europe. Both were placebo-controlled and employed applications BID for 1 week. The adverse events reported for the skin and appendages were as follows.

Adverse events - skin and appendages Lamisil solution BID x 1 week Pityriasis versicolor						
Event	US study		Non-US study		Both studies	
	Lamisil n=98	Placebo n=47	Lamisil n=77	Placebo n=35	Lamisil n=175	Placebo n=82
Abscess	-	-	1 (1.3%)	-	1 (0.6%)	-
Eczema	-	1 (2.1%)	1 (1.3%)	1 (2.9%)	1 (0.6%)	2 (2.4%)
Folliculitis	-	-	1 (1.3%)	-	1 (0.6%)	-
Pruritus	1 (1.0%)	-	2 (2.6%)	1 (2.9%)	3 (1.7%)	1 (1.2%)
Rash	1 (1.0%)	-	-	-	1 (0.6%)	-
Erythematous rash	-	-	2 (2.6%)	-	2 (1.1%)	-
Maculopapular rash	1 (1.0%)	-	-	-	1 (0.6%)	-
Skin disorder	-	1 (2.1%)	-	-	-	1 (1.2%)
Dry skin	-	1 (2.1%)	1 (1.3%)	-	1 (0.6%)	1 (1.2%)
Skin exfoliation	1 (1.0%)	-	-	1 (2.9%)	1 (0.6%)	1 (1.2%)
Application site reaction	1 (1.0%)	1 (2.1%)	-	-	1 (0.6%)	1 (1.2%)

Tinea pedis: Four controlled studies were performed. Study SFF 351 was done in the US, was placebo-controlled, with applications BID for 7 days. Study SFF 301 was done in Europe, was placebo-controlled, with applications QD for 7 days. Study SFF 309 was done in Europe, used a positive control (clotrimazole), with applications BID for 7 days. Study 104 was done in the US, was placebo-controlled, with applications BID for 2 weeks.

The adverse events reported in these studies were as follows.

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Adverse events - skin and appendages Lamisil solution Tinea pedis - Studies 351, 301, 309						
Event	US studies		Non-US studies			
	Lamisil BIDx1wk n=104	Placebo n=49	Lamisil QDx1wk n=113	Lamisil BIDx1wk n=340	Clotri BIDx4wk n=345	Placebo n=57
Contact dermatitis	1 (1.0%)	-	-	-	-	-
Bullous eruption	1 (1.0%)	-	-	1 (0.3%)	-	-
Eczema	1 (1.0%)	-	-	2 (0.6%)	3 (0.9%)	-
Herpes simplex	1 (1.0%)	-	-	1 (0.3%)	-	-
Onychomycosis	-	1 (2.0%)	-	-	-	-
Pruritus	-	-	2 (1.8%)	2 (0.6%)	3 (0.9%)	1 (1.8%)
Erythematous rash	-	-	1 (0.9%)	1 (0.3%)	3 (0.9%)	-
Maculopapular rash	-	-	-	-	-	1 (1.8%)
Pustular rash	-	-	-	1 (0.3%)	1 (0.3%)	1 (1.8%)
Rhagades	-	-	-	5 (1.5%)	1 (0.3%)	-
Seborrhea	1 (1.0%)	-	-	-	-	-
Skin disorder	-	2 (4.1%)	3 (2.7%)	2 (0.6%)	-	3 (5.3%)
Dry skin	-	-	-	-	2 (0.6%)	-
Skin exfoliation	-	-	1 (0.9%)	4 (1.2%)	5 (1.4%)	5 (8.8%)
Application site reaction	1 (2.9%)	-	-	5 (1.5%)	3 (0.9%)	-
Contact dermatitis (application site)	-	-	-	-	1 (0.3%)	-

Adverse events - skin and appendages Lamisil solution Study SFF 104 - tinea pedis		
Event	Lamisil n=42	Placebo n=42
Application site reaction	2 (4.8%)	-
Pruritus	-	1 (0.4%)
Dermatitis	1 (2.4%)	-

Tinea corporis/cruris: Three controlled studies were performed. Study SFF 303 was performed in Europe, Study SFF 105 was done in the US, and Study SFF 108 was done in Brazil; all were placebo controlled, with applications QD for one week. Study SFF 303 is presented separately from the other two studies, as it was performed at a different time, and was of different design and operating procedures. The pooled data for Studies SFF 105 and 108 are provided. Adverse events were as follows.

Adverse events - skin and appendages Lamisil solution Study SFF 303 - tinea corporis/cruris		
Event	Lamisil n=99	Placebo n=48
Application site reaction	1 (1.0%)	2 (4.2%)
Folliculitis	1 (1.0%)	3 (6.3%)
Abnormal pigmentation	2 (2.0%)	-
Pruritus	6 (6.1%)	3 (6.3%)
Rash	1 (1.0%)	-
Erythematous rash	5 (5.1%)	5 (10.4%)
Maculopapular rash	2 (2.0%)	1 (2.1%)
Papular rash	-	1 (2.1%)
Pustular rash	1 (1.0%)	2 (4.2%)
Depigmentation	1 (1.0%)	-
Skin disorder	3 (3.0%)	-
Skin exfoliation	3 (3.0%)	2 (4.2%)
Urticaria	1 (1.0%)	-

Adverse events - skin and appendages Lamisil solution Studies SFF 105, 108 - tinea corporis/cruris		
Event	Lamisil n=67	Placebo n=70
Application site reaction	2 (3.0%)	1 (1.4%)
Surgery	-	1 (1.4%)
Contact dermatitis	-	1 (1.4%)
Furunculosis	-	1 (1.4%)

All indications: The pooled adverse event data for the six SFF 300 series of studies were as follows.

Adverse events - skin and appendages Lamisil solution Series 300 studies - all indications					
Event	Lamisil QD/1wk n=212	Lamisil BID/1wk n=619	Lamisil Total n=831	Clotri BID/4wk n=345	Placebo n=236
Application site reaction	1 (0.5%)	9 (1.5%)	10 (1.2%)	3 (0.9%)	3 (1.3%)
Contact dermatitis application site	-	-	-	1 (0.3%)	-
Contact dermatitis	-	1 (0.2%)	1 (0.1%)	-	-
Abscess	-	1 (0.2%)	1 (0.1%)	-	-
Bullous eruption	-	2 (0.3%)	2 (0.2%)	-	-
Eczema	-	4 (0.6%)	4 (0.5%)	3 (0.9%)	2 (0.8%)
Folliculitis	1 (0.5%)	1 (0.2%)	2 (0.2%)	-	3 (1.3%)
Herpes simplex	-	2 (0.3%)	2 (0.2%)	-	-
Onychomycosis	-	-	-	-	1 (0.4%)
Abnormal pigmentation	2 (0.9%)	-	2 (0.2%)	-	-
Pruritus	8 (3.8%)	5 (0.8%)	13 (1.6%)	3 (0.9%)	5 (2.1%)
Rash	1 (0.5%)	1 (0.2%)	2 (0.2%)	-	-
Erythematous rash	6 (2.8%)	3 (0.5%)	9 (1.1%)	3 (0.9%)	5 (2.1%)
Maculopapular rash	2 (0.9%)	1 (0.2%)	3 (0.4%)	-	2 (0.8%)
Papular rash	-	-	-	-	1 (0.4%)
Pustular rash	1 (0.5%)	1 (0.2%)	2 (0.2%)	1 (0.3%)	3 (1.3%)
Rhagades	-	5 (0.8%)	5 (0.6%)	1 (0.3%)	-
Seborrhea	-	1 (0.2%)	1 (0.1%)	-	-
Depigmentation	1 (0.5%)	-	1 (0.1%)	-	-
Skin disorder	6 (2.8%)	2 (0.3%)	8 (1.0%)	-	6 (2.5%)
Dry skin	-	1 (0.2%)	1 (0.1%)	2 (0.6%)	1 (0.4%)
Skin exfoliation	4 (1.9%)	5 (0.8%)	9 (1.1%)	5 (1.4%)	8 (3.4%)
Urticaria	1 (0.5%)	-	1 (0.1%)	-	-

Five patients discontinued treatment due to adverse events related to the study medication; of these, two were in the Lamisil group, one was in the clotrimazole group, and one was in the placebo group. All occurred in foreign studies. In the Lamisil group one patient reported a worsened erythema and desquamation accompanied by pustules and vesiculation, and one patient reported a worsened erythema and pruritus accompanied by incrustation and vesiculation. In the clotrimazole group one patient discontinued due to burning. In the placebo group one patient reported burning with worsened erythema and desquamation accompanied by pruritus and pustules. There were no serious adverse events that were related to the study medications.

b) Controlled studies on other indications.

Two placebo controlled studies were performed in candidiasis; Study SFF 306 was performed in Mexico and Study SFF 311 was performed in Central and South America. Both studies employed 7 days of QD applications. The pooled adverse events related to the skin and appendages in these studies were as follows.

Adverse events - skin and appendages Lamisil solution Cutaneous candidiasis		
Event	Lamisil n=174	Placebo n=85
Application site edema	1 (0.6%)	-
Application site reaction	28 (16.1%)	19 (22.4%)
Eczema	2 (1.1%)	-
Folliculitis	-	1 (1.2%)
Furunculosis	1 (0.6%)	-
Hyperkeratosis	1 (0.6%)	-
Pruritus	6 (3.4%)	2 (2.4%)
Erythematous rash	4 (2.3%)	2 (2.4%)
Maculopapular rash	1 (0.6%)	-
Rhagades	1 (0.6%)	1 (1.2%)
Skin discoloration	-	1 (1.2%)
Skin disorder	2 (1.1%)	2 (2.4%)
Dry skin	1 (0.6%)	-
Skin exfoliation	4 (2.3%)	1 (1.2%)
Skin ulceration	-	1 (1.2%)

Two patients in the Lamisil group and one patient in the placebo group discontinued due to dermatologic adverse events. The events were not specified, but were reported as severe and as definitely attributed to the drug. Resolution occurred in the two Lamisil patients.

Two placebo controlled studies were performed in seborrheic dermatitis; these were Study SFF 304 and Study 352, both performed in the US and Canada. Both studies employed two weeks of QD applications. The pooled adverse events related to the skin and appendages in these studies were as follows.

Adverse events - skin and appendages Lamisil solution Seborrheic dermatitis		
Event	Lamisil n=79	Placebo n=80
Application site reaction	7 (8.9%)	12 (15.0%)
Acne	-	1 (1.2%)
Contact dermatitis	-	1 (1.2%)
Hemorrhagic dermatitis	-	1(1.2%)
Herpes zoster	1 (1.3%)	1 (1.2%)
Pruritus	5 (6.3%)	7 (8.8%)
Psoriaform rash	1 (1.3%)	1 (1.2%)
Skin disorder	1 (1.3%)	1 (1.2%)
Dry skin	2 (2.5%)	2 (2.5%)

One patient in the Lamisil group and two patients in the placebo group discontinued due to dermatologic adverse events. These were moderate to severe contact dermatitis and burning with redness; all of these events resolved.

c) Uncontrolled studies.

Study SFF 106, conducted in Sweden, was on the treatment of scalp seborrheic dermatitis, and employed QD applications for 28 days. Of 22 patients treated with Lamisil, 2 patients (9%) reported dry skin.

Two studies on the treatment of dermatomycoses were performed in Japan; these employed QD applications for 4 weeks in tinea pedis, and for 2 weeks for other dermatomycoses. Of 112 patients treated with Lamisil, 4 experienced adverse events, which were described as an 'irritated sensation'.

d) Clinical pharmacology studies.

Eight clinical pharmacology studies were performed on 1% Lamisil solution. The design of the studies and the numbers of subjects were as follows.

Clinical pharmacology studies		
Study #	Test	# pts
Percutaneous absorption		
SFF 101		11
SFF 103		10
Tissue pharmacokinetics		
SFF 307		38
Tolerability		
SF 0058	Cumulative irritancy potential (occlusion)	28
SFF 102	Cumulative irritancy potential (occlusion and semi-occlusion)	25
SFF 701	Cumulative irritancy potential (occlusion and semi-occlusion)	25
SFF 107	Phototoxicity	10
	Photoallergy	31
	Sensitization potential	192
SFF Japan-CP	Sensitization Photosensitization	24

The only adverse event related to the skin and appendages was erythema in 4/24 subjects in Study SFF Japan-CP; this also occurred in the placebo groups. There were no serious adverse events or discontinuations due to the study drug.

The results of the percutaneous absorption studies showed that low plasma concentrations of terbinafine follow topical administration of Lamisil solution, irrespective of skin condition or surface area of application. Plasma concentrations reached a maximum of 2.5% of those following the 250 mg daily

dosing approved for Lamisil tablets. Administration of 1% Lamisil solution for 7 days yielded tissue levels which were similar whether administered by dropper or spray, and were similar to those with Lamisil cream.

Study SFF 0058 showed irritation potential under the test conditions for both Lamisil solution and the vehicle. This was thought to be due to the occlusive patches used, and so additional studies SFF 102 and SFF 107 were conducted, using both occlusive and semi-occlusive patches. These did not confirm the potential for irritation shown in the first study. The results of the cutaneous tolerability studies showed no potential for irritancy, contact sensitization, photoallergic sensitization, or phototoxicity.

2) Updated Integrated Summary of Safety

a) Analysis of safety data for tinea cruris.

The adverse events which occurred in the three pivotal clinical studies on tinea cruris/corporis are provided separately for each diagnosis. Those events which involved the skin and appendages were as follows.

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Adverse events - Studies 105, 108, 303 Skin and appendages						
Adverse event	Tinea cruris		Tinea corporis		Both	
	Lamisil n=78	Placebo n=52	Lamisil n=61	Placebo n=44	Lamisil n=27	Placebo n=21
Contact dermatitis	-	-	-	-	-	1 (4.7%)
Folliculitis	-	-	1 (1.6%)	2 (4.5%)	-	1(4.7%)
Furunculosis	-	-	-	-	-	1 (4.7%)
Abnormal pigmentation	1 (1.2%)	-	1 (1.6%)	-	-	-
Pruritus	4 (5.1%)	1 (1.9%)	1 (1.6%)	1 (2.3%)	1 (3.7%)	1 (4.7%)
Rash	-	-	1 (1.6%)	-	-	-
Erythematous rash	4 (5.1%)	2 (3.8%)	-	1 (2.3%)	1 (3.7%)	2 (9.5%)
Maculo-papular rash	1 (1.2%)	-	-	1 (2.3%)	1 (3.7%)	-
Papular rash	-	-	-	-	-	1 (4.7%)
Pustular rash	1 (1.2%)	-	-	1 (2.3%)	-	1 (4.7%)
Depigmentation	-	-	1 (1.6%)	-	-	-
Skin disorder	1 (1.2%)	-	-	-	1 (3.7%)	-
Exfoliation	3 (3.8%)	-	-	1 (2.3%)	-	1 (4.7%)
Urticaria	-	-	1 (1.6%)	-	-	-
Application site reaction	3 (3.8%)	2 (3.8%)	-	-	-	1 (4.7%)

b) Adverse event reports.

a. Novartis worldwide safety data base.

A summary of spontaneous adverse event information from the worldwide safety database maintained by Novartis Pharma Ltd. is provided; this is intended to update the Integrated Summary of Safety submitted in NDA 20-749. Reports on both terbinafine HCL solution 1% and terbinafine HCL cream 1% are provided. These data include Periodic Safety Update Reports which cover the period from October 1990 to March 31, 1998, and the Periodic Adverse Drug Experience Reports for Lamisil cream for the period from December 1997 to December 1998, and for Lamisil solution from October 1997 to January 1999.

1. Lamisil solution. There have been no deaths or serious adverse events reported for Lamisil solution. The adverse events involving the skin and appendages during 1997 and 1998 were as follows.

Adverse event reports * Lamisil solution Skin and Appendages	
Event	# events
Application site reaction	1
Exfoliative dermatitis	1
Nail disorder (discoloration)	2
Rash	1
Skin disorder	1
Vesiculobullous rash	1
* Novartis worldwide safety data base	

2. Lamisil cream. The adverse events involving the skin and appendages reported from October 1990 through March 1998 were as follows.

Adverse event reports * Lamisil cream Skin and Appendages	
Event	# events
Skin disorder	1
Angioedema	3
Application site reaction	16
Contact dermatitis	18
Dry skin	3
Eczema	3
Epidermal necrolysis	1
Erythema multiforme	3
Exfoliative dermatitis	3
Fungal dermatitis	1
Maculopapular rash	7
Pruritus	15
Psoriasis	6
Pustular rash	1
Rash	40
Benign neoplasm	1
Skin discoloration	5
Skin disorder	5
Skin hypertrophy	1
Skin striae	1
Skin ulcer	3
Stevens Johnson syndrome	1
Sweating	1
Urticaria	6
Vesiculobullous rash	7
* Novartis worldwide safety data base	

One additional event which occurred during clinical trials and is not included in the above tabulation was an application site reaction with erythema, pruritus and swelling.

Ten cases of serious adverse events were reported in patients who were being treated with Lamisil cream. Only one of these cases appears to be possibly related to Lamisil. This patient was treated for tinea pedis, and after one day of treatment was hospitalized with an exanthematous pustulosis. The medication was discontinued and the patient recovered in about three weeks.

c) FDA Spontaneous Reporting System

The sponsor tabulated the reports from the FDA Spontaneous Reporting System (SRS), which includes reports received through October 31, 1997, and are the most recent data that are publicly available. This cutoff date is at the time of the approval of Lamisil solution, so that none of the reports are associated with use of the solution. The reports are presumed to be associated with use of Lamisil cream, and probably include a few cases in which Lamisil tablets were administered.

Cases which have not been included in the tabulation of the Novartis Worldwide Safety database are described below. The adverse event reports involving the skin and appendages are as follows.

Adverse event reports * Lamisil formulations other than solution Skin and Appendages	
Event	# events
Application site reaction	2
Contact dermatitis	1
Maculopapular rash	2
Pruritus	1
Rash	5
Urticaria	1
* FDA Spontaneous Reporting System	

Five cases in the SRS that were not in the Novartis database were

designated as having used topical terbinafine; one of these, a rash and 'possible contact dermatitis' had an outcome (hospitalization) that would label it as serious. This patient was on several concomitant systemic medications, including ketoconazole.

d) World Health Organization adverse event data

At the request of the sponsor the WHO monitoring center conducted a search of its drug safety database for cases in which topical terbinafine was entered as the suspect drug. The search covered the time from the inception of the database in 1968 to June 17, 1998. Presumably the majority of reports represent adverse events with terbinafine cream, since the solution was not marketed until February 27, 1998.

The total adverse event reports which involved the skin and appendages were as follows.

Total adverse event reports * Topical terbinafine Skin and Appendages	
Event	# events
Application site reaction	13
Contact dermatitis	5
Dry skin	2
Erythema multiforme	1
Maculopapular rash	1
Pruritus	4
Rash	22
Skin discoloration	1
Skin disorder	2
Skin ulcer	1
Urticaria	1
Vesiculobullous rash	4
* WHO adverse event data	

Those adverse events that were reported directly to national centers outside the US and then to WHO (included in the above

tabulation) represent data not previously presented to the FDA; these were as follows.

Adverse event reports outside the US * Topical terbinafine Skin and Appendages	
Event	# events
Application site reaction	4
Dry skin	1
Erythema multiforme	1
Maculopapular rash	1
Pruritus	2
Rash	7
Urticaria	1
Vesiculobullous rash	2
* WHO adverse event data	

3) Fungal resistance

In response to a request by the Agency at the pre-NDA meeting, the sponsor has addressed the question of the development of secondary or acquired resistance to terbinafine with the chronic use of terbinafine in the treatment of tinea pedis, tinea cruris, or tinea corporis.

The sponsor differentiates between clinical resistance and *in vitro* resistance. Clinical resistance is defined as the persistence or progression of an infection despite antimicrobial therapy. Factors involved in clinical resistance are the host defenses, a possible protected reservoir of pathogenic organisms in the host, the adequacy of drug delivery, including patient compliance, and, for topical medications, the dermal penetration and dermal persistence of the active ingredient.

In vitro resistance is broken down into two types, namely, primary resistance, defined as resistance to the antimicrobial before there has been any exposure to it, and secondary (acquired) resistance, defined as resistance to an antimicrobial that develops after exposure to the drug.

The sponsor states that there are no documented reports of secondary resistance to either oral or topical terbinafine in clinical isolates of dermatophytes or any other fungal pathogen, despite an estimated total human exposure that now exceeds 70 million patients since the initial approval of terbinafine in Great Britain in 1990.

There have also been no reports of secondary resistance to any of the other allylamines, nor have there been reports of resistance to the thiocarbamates, which have the same mechanism of action as the allylamines and have been widely available since the 1970's.

A report is presented on the antifungal susceptibility profile of terbinafine by M.A. Ghannoum, Ph.D., Center for Medical Mycology, University Hospitals of Cleveland, Case Western Reserve University. This states that information on the antifungal susceptibility of terbinafine has been limited, which may be attributed to the lack of a suitable method for determining the susceptibility of dermatophytes to terbinafine. Therefore, their group, under the Auspices of the National Committee for Clinical Laboratory Standards, developed a method to determine the antifungal susceptibility of dermatophytes to terbinafine, griseofulvin, itraconazole, and fluconazole. This method was used in the following studies.

1. Antifungal susceptibility pattern of terbinafine against clinical dermatophyte isolates.

   The objectives of this study were to determine the antifungal susceptibility pattern of terbinafine against clinical isolates of dermatophytes, and to compare terbinafine activity with that of other currently used antifungal agents.

   Two hundred sixteen dermatophyte clinical isolates were obtained from the culture collection at the Center for Medical Mycology. These isolates included 132 *T. rubrum*, 32 *T. mentagrophytes*, 42 *T. tonsurans*, 7 *M. canis*, and 3 *E. floccosum*. The following antifungals were used in powder form and diluted according to the manufacturer's directions, using a microdilution broth assay: terbinafine, itraconazole, fluconazole, and griseofulvin. The results showed that 100% of the isolates were inhibited at levels of 0.03 ug/ml of terbinafine, 1 ug/ml of itraconazole, 4 ug/ml of griseofulvin, and 32 ug/ml of fluconazole. Resistance to terbinafine was not detected in any of the clinical isolates assayed.

2. Determination of the antifungal susceptibility of dermatophyte and non-dermatophyte isolates obtained from the nails of subjects participating in an epidemiological survey of onychomycosis.

   It was felt that a determination of the antifungal susceptibility of terbinafine against organisms isolated from the general population would reveal whether there are resistant isolates present in a population which was not pre-exposed to the drug.

   One thousand eight hundred and thirty-two subjects attending a primary care physician's office were screened for onychomycosis during the period from June 1997 to May 1998. Subjects who were there to seek treatment for tinea pedis or onychomycosis were excluded.

   The susceptibilities of 116 dermatophyte isolates were tested; this included 82 *T. rubrum and* 32 *T. mentagrophytes isolates*. The MIC_{90} (ug/ml) was .002 for terbinafine, 4.0 for fluconazole, .125 for itraconazole, and .5 for griseofulvin. Terbinafine resistant isolates were not detected among the dermatophytes obtained from these subjects.

3. Antifungal susceptibility and genetic relatedness of sequential *T. rubrum* strains isolated from patients with onychomycosis treated with terbinafine.

   In addition to the method for determining the antifungal susceptibility of dermatophytes, the author developed a method to use a random amplified polymorphic DNA technique for the molecular subtyping of *T. rubrum*. These methods were used to determine whether persistence of infection might result from acquisition of antifungal resistance or re-infection with a new *T. rubrum* strain.

   The objectives of this study were a) to examine the strain relatedness between sequential *T. rubrum* isolates obtained from patients with onychomycosis who were treated with terbinafine for an extended period of time (up to 24 weeks), and b) to determine the susceptibility of sequential *T. rubrum* isolates using a microdilution broth method.

   Approximately 1500 patients with onychomycosis from 300 sites in the US were enrolled in a study to evaluate the safety and effectiveness of 12, 18, and 24 weeks of therapy with 250 mg/day of terbinafine. Thirty-eight patients whose cultures were positive for *T. rubrum* at visits 2 to 8 throughout the

study were chosen for evaluation. The isolates from each of the patient visits, or a total of 82 isolates, were tested against terbinafine, and against fluconazole, itraconazole, and griseofulvin.

Results of susceptibility testing were that in all cases studied, there was no change in MIC over time in the sequential isolates obtained from the same patient at different visits. The MIC's of terbinafine against all *T. rubrum* isolates were with one exception either identical or within one dilution (MIC values were between < 0.001 and 0.015 *ug*/ml, except for one patient.) Similarly no change was seen in the susceptibility of the other antifungals.

DNA typing has been completed on 29 sets of patient isolates. A similar amplification pattern was found in all the fungal isolates tested, which suggests that the same strain is responsible for the infection, that is, that re-infection with new strains did not occur.

The conclusion was that failure of the patients to clear onychomycosis was not related to resistance development in *T. rubrum* nor to re-infection with new strains.

4) Other sources of safety information

a. American Association of Poison Control Centers data base. The sponsor commissioned a report from ——————→ on human single substance exposures to terbinafine cream 1%, and for comparison to miconazole 2% cream and to clotrimazole 1% cream. (For policy reasons the AAPCC provided data only on the combination of miconazole and clotrimazole rather than the single substances.) The report was based on data voluntarily reported to poison control centers from 1993 through 1997. Data from 1998 were not available at the time of the report, and no data were available for terbinafine solution. The total number of cases reported with terbinafine alone were 203, and with the comparative drugs were 1,747.

The ages of the patients were as follows.

Patient Ages Reports to American Association of Poison Control Centers					
	Infant	Child	Teen	Adult	Unknown
Terbinafine	79 (38.9%)	83 (40.9%)	2 (1.0%)	38 (18.7%)	1 (0.5%)
Comparative drugs*	829 (47.5%)	634 (36.3%)	41 (2.3%)	231 (13.2%)	12 (0.7%)
* miconazole and clotrimazole					

The route of exposure was as follows.

Routes of exposure Reports to American Association of Poison Control Centers					
	Ingestion	Dermal	Ocular	Other	Multiple
Terbinafine	157 (77%)	17 (8%)	11 (5%)	6 (3%)	12 (6%)
Comparative drugs*	1542 (88%)	46 (3%)	27 (2%)	42 (2%)	90 (5%)
* miconazole and clotrimazole					

The occurrence of symptoms was as follows.

Occurrence of symptomatology Reports to American Association of Poison Control Centers					
	Ingestion	Dermal	Ocular	Other	Multiple
Terbinafine					
No symptoms	155 (99%)	13 (77%)	3 (27%)	5 (83%)	10 (83%)
Related symptoms	2 (1%)	4 (24%)	8 (73%)	1 (17%)	2 (17%)
Comparative drugs *					
No symptoms	1503 (98%)	36 (78%)	7 (26%)	32 (76%)	83 (92%)
Related symptoms	39 (3%)	10 (22%)	20 (74%)	10 (24%)	7 (8%)
* miconazole and clotrimazole					

No major effects or deaths were reported in either group. The proportion of patients who were treated at the exposure location was 95% in the terbinafine group and 97% in the comparative group. Of a total of 7 patients in the terbinafine group who were treated at a health care facility, 6 were treated and released and 1 was lost to followup.

The clinical effects which were considered to be related to drug exposure were as follows.

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Clinical effects related to drug exposure Reports to Americal Association of Poison Control Centers		
	Terbinafine	Comparative
Cardiovascular		
Cardiac arrest	-	1
Dermal		
Edema	-	2
Erythema/flushed	-	2
Hives	1	2
Irritation/pain	3	5
Pruritus	2	1
Stinging	-	1
Rash	1	3
Gastrointestinal		
Abdominal pain	1	3
Nausea	1	7
Oral irritation	-	8
Throat irritation	-	2
Vomiting	-	18
Neurologic		
Dizziness/vertigo	-	2
Headache	-	1
Ocular		
Blurred vision	1	-
Ocular irritation/pain	8	24
Lacrimation	1	1
Respiratory		
Cough/choke	1	2
Respiratory arrest	-	1
Miscellaneous		
Pain	-	1
Other	3	8

The sponsor states that, in summary, no cases involving terbinafine resulted in major toxic effects or death. Intentional misuse of the product is almost non-existent, and there was a low level of toxicity with accidental exposure. Among the terbinafine cases with a known outcome, all but one had either minor or no medical effects. The single exception was judged to have moderate effects. For the cases reported to a Poison Control Center the risk of serious medical effects with exposure to terbinafine or to the comparison drugs appears to be quite low.

b. Other clinical trials of terbinafine solution.

One additional clinical trial of terbinafine HCl solution 1%, Study SFF 310, was completed following submission of the NDA for prescription status; this was as follows.

This was a double blind, randomised, controlled, single center comparison of Lamisil solution 1% administered BID for one week and clotrimazole solution 1% administered BID for four weeks in patients with tinea pedis. The study was conducted in the Bejing Medical Hospital, Bejing, China. A total of 248 patients in each group comprised the population evaluated for safety.

The adverse events related to the skin and appendages were as follows.

Adverse events - Study SFF 310 Skin and appendages		
	Terbinafine n=248	Clotrimazole n=248
Contact dermatitis	1	-
Erythema multiforme	1	-
Pruritus	1	-
Psoriaform rash	1	-
Skin ulceration	1	-

The five patients on terbinafine with adverse events of the skin were withdrawn from the study due to the adverse events. All had local skin reactions. There were no serious adverse events related to the study medications.

c. Literature review.

A review of the medical literature pertinent to the safety of topical terbinafine was performed using the National Library of Medicine MEDLINE database, for the period from 1996 to March 1999. Only one relevant article was identified; this was Bakos, L. et al, "Open clinical study of the efficacy and safety of terbinafine cream 1% in children with tinea corporis and tinea cruris", Pediat Infect Dis. J 1997; 16: 545-6. In this open trial of 97 children aged 2 to 15, terbinafine cream was applied QD for one week. Adverse events were reported in five children; these were itching in 3, itching and exacerbation of erythema in 1, and contact dermatitis in 1.

Sponsor's conclusions

The sponsor states in conclusion that "Terbinafine HCl solution 1% is a safe, effective topical antifungal agent for the treatment of tinea pedis and tinea corporis/cruris. An updated review of adverse event reports from Novartis, the WHO, and the FDA SRS showed no secular or temporal trends in the distribution of reports. A review of data available regarding the risk of emergence of resistant fungi as a result of the possible OTC availability of terbinafine showed no evidence for concern. Lastly, a review of the published medical literature revealed no new or unexpected safety-related issues.

Coupled with the information provided in the original NDA for terbinafine HCl solution 1% (NDA 20-749), this supplement supports the application for the approval of OTC status for terbinafine HCl solution 1%."

Response to request for additional information

It was noted by this reviewer that the terminology for a number of the adverse events reported is ambiguous and could connote a significant event, and therefore it was felt that the specific nature of such events should be described, if possible. These events include bullous and vesiculobullous eruption, skin disorder, exfoliative dermatitis, and angioedema, reported both in the controlled clinical studies and in the various safety databases. In addition, further information on the single cases each of Stevens Johnson syndrome and epidermal necrolysis with Lamisil cream in the Novartis Worldwide safety database would be desirable.

A request was made of the sponsor on October 6, 1999, to provide additional information on these particular adverse events. In

their response of October 21, 1999, the sponsor states that they were assured in the pre-NDA meeting that all that was required for safety purposes in consideration of the NDA was an update of safety information for topical Lamisil. It was their understanding that the safety review for the OTC Lamisil solution NDA would not require them to revisit cases which were included in the original submission. Therefore, in response they have provided additional information only on events in their databases. This includes one case each of exfoliative dermatitis, skin disorder, and vesiculobullous rash with Lamisil solution, and the following cases with Lamisil cream: vesiculobullous rash in 7, skin disorder in 6, exfoliative dermatitis in 3, erythema multiforme in 3, angioedema in 3, epidermal necrolysis in 1, and Stevens Johnson syndrome in 1.

The sponsor further states that the precise criteria for the FDA definition of a 'serious' adverse event was rigorously applied to the available cases and data, and that no serious cases with Lamisil solution were identified in the Novartis Worldwide Safety database.

Review of the three events reported with Lamisil solution reveals that two of the events, exfoliative dermatitis and vesiculobullous rash, occurred in the same patient. As further described, the patient had blistering after application of Lamisil to the toes for 15 days, with subsequent exfoliation of the toes. Resolution occurred within one month. The event in the other patient, reported as skin disorder, is further described as sore, tender skin after using the spray for five days.

The reported events with Lamisil cream are either apparently unrelated to use of the cream, or the information given is too meager to determine causality.

Labeling review

The claim that the product cures athlete's foot, jock itch, and ringworm should be modified to reflect the level of therapeutic effect. Also, the following statement should be re-worded for greater clarity: "Stop use and ask a doctor if too much irritation occurs or gets worse." However, these claims and the statement cited are on the approved OTC labeling for Lamisil cream.

A pediatric supplement is needed, as the proposed container label includes directions for use for those 12 years of age and older.

Except for the method of administration as described respectively for the spray and the cream, the proposed OTC label for Lamisil pump spray is identical to the approved OTC label for Lamisil cream.

Summary and evaluation

Since approval in 1997, approximately 1.7 million bottles of terbinafine hydrochloride solution 1% have been sold worldwide. In the US, where the product was launched in 1998, [redacted] bottles have been sold.

In support of the prescription to OTC switch for Lamisil solution the sponsor has provided synopses of the pivotal clinical studies in NDA 20-749 together with additional analyses of the results of these studies, an updated Integrated Summary of Safety, and a report on fungal resistance to terbinafine HCl, as follows.

1) Effectiveness data: Two adequate and well controlled studies were performed on interdigital tinea pedis, and three adequate and well controlled studies were performed on tinea corporis/cruris. The studies included a one week treatment period and a seven week followup period.

The efficacy parameters were mycology (KOH exam and culture), scoring of clinical signs and symptoms, and a clinical assessment by the patient and physician. The results were presented as the percentage of patients with a) a mycological cure, defined as a negative KOH and culture, b) an 'Effective Treatment', defined as a mycological cure and a total clinical score representing minimal residual signs and symptoms, and c) a 'Complete Cure', defined as a mycological cure and a complete absence of all signs and symptoms. The primary efficacy variable was the percentage of patients with an 'Effective Treatment.'

The results of the studies were as follows.

Tinea pedis: In both studies the results for the ITT population at the end of the study showed a significant superiority of Lamisil solution over the vehicle in the percentage of patients with an Effective Treatment and with a Complete Cure. Additional analyses of the MITT populations showed similar results.

Tinea corporis/cruris: In all three studies the results for the ITT population at the end of the study showed a significant superiority of Lamisil solution over the vehicle in the percentage of patients with an Effective Treatment and with a

Complete Cure. Additional analyses of the MITT populations showed similar results.

2) Safety data: For the adverse events which occurred in the controlled studies, the tabulation of events separately for tinea cruris and corporis showed a higher incidence of local reactions, as would be expected, in the tinea cruris group, particularly pruritus, rashes, and application site reactions.

Reports of adverse events in the Novartis Worldwide safety database for Lamisil solution during 1997 and 1998 have involved single cases of a few events, despite the large distribution of the product during this time. None of these were serious events.

Conclusions: It is felt that the data on the safety of Lamisil solution 1% provided in this NDA are adequate to support the OTC use for tinea pedis, tinea cruris, and tinea corporis.

Recommendations: It is recommended that this NDA be approved for the OTC use of Lamisil solution 1% in athlete's foot (tines pedis), jock itch (tinea cruris), and ringworm (tinea corporis).

/S/

Phyllis A. Huene, M.D.

1/10/99

cc: Orig NDA 21-124
HFD-540 Division files
HFD-540/Wilkin /S/ 1/14/00
HFD-540/Walker
HFD-540/Huene
HFD-540/White
HFD-540/MO/HFD-560 /S/ 1/31/00
HFD-540/Vidra
HFD-540/Hill
HFD-540/Al-Osh

/S/ 3/17/00